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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,356	12/11/2006	Richard R. Bott	DOG 0101 PA/35319.68	9374

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DINSMORE & SHOHL LLP
FIFTH THIRD CENTER, ONE SOUTH MAIN STREET
SUITE 1300
DAYTON, OH 45402-2023

EXAMINER	
PARK, HAEJIN S	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,356	BOTT ET AL.	
	Examiner	Art Unit	
	H. SARAH PARK	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *72 and 74-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *72, 74-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendments and arguments filed on February 18, 2011 are acknowledged and have been fully considered. Claims 1 – 71 and 73 are cancelled and claims 72 and 81 are amended. Claims 72 and 74 – 91 are pending and under consideration.

OBJECTIONS/REJECTIONS WITHDRAWN

No rejection in the previous Office Action is withdrawn.

OBJECTIONS/REJECTIONS MAINTAINED

The rejection of claims 72 and 74 – 91 under 35 U.S.C. 103(a) based on Kosal and Bott et al. is maintained.

Claim Rejections - 35 USC § 103 (Maintained)

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

1. Claims 72 and 74 – 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kosal (US Patent no. 6,545,086 issued on April 8, 2003) in view of Bott et al. (US Pre-Grant Publication no. 2003/0180281 A1 published on September 25, 2003) as evidenced by Woodard et al. (US Patent no. 4,655,767 issued on April 7, 1987).

2. Kosal is directed to oil-in-water (O/W) emulsions comprising a silicone phase with pressure sensitive adhesives (PSAs) in a continuous water phase, and a surfactant (Title; abstract; claim 1).

Concerning claim 72, Kosal teaches that the O/W emulsions are preferably produced by phase inversion and using a surfactant (col.4 ll.24-32). The aqueous or hydrophilic phase of the O/W emulsion contains a carrier referred to as a "thickener" including a water soluble polymer such as polyvinyl alcohol (col.5 ll.4-13). Kosal further teaches avoidance of hydrocarbon based, i.e. lipophilic, solvents in medical applications such as transdermal drug delivery patches (col.5 ll.26-28). Kosal also teaches that the O/W emulsions can be used as release-modifying additives and in medical applications such as transdermal drug delivery patches (col.1 ll.20-23; col.5 ll.23-24).

Concerning claim 74, Kosal teaches the use of a surfactant in forming the O/W emulsions while shearing in the phase inversion process (col.4 l.27). By its nature the surfactant forms between the hydrophilic and hydrophobic phases to aid formation and stabilization of an emulsion.

Concerning claims 75 – 76, Kosal teaches using polyvinyl alcohol, among other polymers, as a thickener in the aqueous phase of the O/W emulsion as discussed above (col.5 ll.4-13). Polyvinyl alcohol is water soluble and thus in the aqueous phase of the emulsion.

Concerning claims 81 – 82, Kosal discloses the use of a dispersing agent, i.e. a surfactant, in the inverted mixture and another in the aqueous phase, wherein a more hydrophobic surfactant is added to the oily phase and a less hydrophobic surfactant is

added to the aqueous phase (col.4 ll.27-35). Kosal also teaches siloxane-based nonionic surfactants (col.4 ll. 11-12).

Concerning claims 83 – 84, Kosal teaches emulsion comprising silicone PSAs formed from silicone resins (col.2 ll.31-34; col.4 ll.24-25).

Concerning claim 85, Kosal teaches that the silicone PSAs generally comprise a product of mixing a silanol-terminated polydiorganosiloxane such as polydimethylsiloxane with a silanol-containing silicone resin, i.e., hydroxy functional silicate resin (col.2 ll.31-40, 45-49).

Concerning claim 86, Kosal teaches with reference to Woodard et al. that silicone PSAs made by mixing the silanol-terminated polydiorganosiloxane and silanol-containing silicone resin may be chemically treated to react the silanol groups with endblocking agents which introduce triorganosilyl or triorganosiloxy units such as trimethylsiloxy units (col.3 ll. 33-37) as taught by Woodard et al. (The '767 patent at col.2 ll.29-45). Kosal further explains that the endblocking agent reduces the sensitivity of the adhesive to loss of adhesion in contact with amines (col.3 ll.41-43).

3. Kosal does not specifically teach the hydrophilic phase of the O/W comprising a protein active agent as recited in claim 72.

Bott et al. teaches water-in-oil (W/O) emulsions comprising a protein active agent in an aqueous phase comprising a carrier such as polyvinyl alcohol, and is directed to sustained release preparations for topical administration of active agents comprising the W/O emulsion wherein the external phase may be silicon PSA taught by Kosal (Title;

abstract; paras.0002, 0008, 0041). Bott et al. teaches furthermore that silicone surfactants can be added to emulsify the internal phase into very small droplets and enhance the release of the active agent (para.0008), as recited in instant claim 82.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Kosal and Bott et al. and prepare O/W emulsions comprising the hydrophobic phase with silicone PSA taught by Kosal for transdermal delivery of protein active agents.

One would have been motivated to do so since Kosal teaches that the silicone PSA provides controlled tack and lubrication and greater durability, free of hydrocarbon based solvents, and enables holding of the active to the skin surface (col.5 ll.14, 17-20, 23-27), which the skilled person would recognize as advantageous in prolonged transdermal drug administration. Kosal further teaches that use of endblocking agents is especially useful for preventing loss of adhesion when the silicone PSA is in contact with amines, comprising proteins (col.3 ll.33-43), and that preferably the O/W emulsions are prepared by phase inversion of an W/O emulsion (col.4 ll.24-32) such as of Bott et al. Bott et al. on the other hand discloses that use of emulsions comprising a silicone PSA (such as of Kosal) and an aqueous phase with protein active agent and a carrier is advantageous for sustained release of the active agent (para.0001, 0002, 0041).

4. Concerning claims 77 – 80 and 91 Kosal does not specifically disclose silicone O/W emulsions comprising an enzyme or a biomolecule recited in claim 91 as an active agent.

Bott et al. however teaches inclusion of various natural, synthetic, and engineered enzymes such as oxidoreductases and transferases, and antibodies, hormones, and biological modulators (para.0029) as well as various proteases (para.0049) as suitable active agents.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Kosal and Bott et al. and prepare O/W emulsion of Kosal for transdermal patches for delivering enzyme active agents taught by Bott et al.

As discussed above, one would have been motivated to do so since Kosal teaches that the silicone PSA provides diverse advantages for use in transdermal medical patches (col.5 ll.14, 17-20, 23-27). Thus applying the O/W emulsion as taught by Kosal to topical delivery of specific types of enzymes as taught by Bott et al. would have been obvious to a person of ordinary skill in the art.

5. Concerning claims 87 – 88, Kosal and Bott et al. do not explicitly disclose multi-layer dressing comprising a controlled-release layer, an adhesive layer, and an additional layer. However as noted above Kosal teaches using the O/W emulsion composition of its invention in prolonged "transdermal delivery patches" (col.4 l.24). Such transdermal drug delivery systems comprising at least three layers were "well known to those skilled in the art" at the time of the invention as evidenced by Woodard et al. (col.3 ll.33-50). Woodard et al. specifically teaches transdermal drug delivery device embodiment with amine-resistant silicone adhesives (Title; abstract; Figs. 1-2).

Specifically the transdermal device shown in Figure 2 of Woodard et al. comprises a drug reservoir layer 20, an adhesive layer 22, and additional layers comprising a backing layer 14 and polymeric material layers 11 and 12 (Fig. 2). When the drug reservoir layer is adjacent to the substrate, i.e., skin, the polymer layer 11 is disposed adjacent to the adhesive layer 22 and spaced from the drug reservoir layer.

Accordingly, in view of the rejection of claim 72 based on Kosal and Bott et al. above and the state of the art as evidenced by Woodard et al., the multilayer controlled composition in the form of a multi-layer dressing in claims 87 - 88 are not patentable.

6. Concerning claim 89, Kosal does not explicitly teach multi-layer dressings comprising dry controlled-release layer of the O/W emulsion.

Bott et al. however teaches preparation of patch comprising silicone PSA emulsion comprising protein active agent and carrier solution, which is spread onto a Mylar® sheet, dried, and then cut into patches (Examples 7-10; paras.0085, 0089, 0093, 0097).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Kosal and Bott et al. and dry the layer comprising composition of instant claim 72.

One would have been motivated to do so because Bott et al. is drawn to transdermal delivery of proteins via patches. In particular the multi-layer patches of Bott et al. were tested for enzymatic stability or loss of activity, and were shown to provide more stable means of storing and releasing the enzyme (paras.0088, 0092, 0096,

0100). Accordingly claim 89 is not patentable in view of the rejection of claim 72 based on Kosal and Bott et al. above.

7. Concerning claim 90, Kosal does not explicitly teach method of delivering the controlled release composition of claim 72 to a substrate.

As discussed above however Kosal and Bott et al. in combination teach delivery of proteins via inverted emulsions comprising silicone with the active in the aqueous phase. Bott et al. further teaches applying the emulsion to a dressing suitable for application directly to skin to protect or administer medicaments to it (para.0025).

It would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the O/W emulsion from combination of Kosal and Bott et al. to a dressing, and apply the dressing to a substrate such as skin since transdermal drug delivery by patches was long known in the art as evidenced by Woodard et al. (Figs.1-2) and referenced by Kosal (col.5 l.24).

Response to Arguments

8. The Applicant's arguments filed on February 18, 2011 have been fully considered but they are not persuasive.

The Applicant argues that "Kosal is directed to a silicone-based pressure sensitive adhesive" and it is "silent concerning any controlled release properties of his pressure sensitive adhesive composition" as in "sustained release," not "adhesive release characteristics" (Remarks at 6, 9). (Hereinafter the term "sustained release" is

used to refer to the claim element "controlled-release".) The Applicant also disagreed with the examiner's "interpretation of Kosal with respect to any teaching concerning controlled release of an active agent" (Remarks at 6).

This argument is not persuasive for the following reasons. While Kosal is indeed directed to a silicone-based pressure sensitive adhesive composition, Kosal amply and specifically discloses using the composition in prolonged medical application in the form of "transdermal delivery patches", i.e., "**to hold an active material** such as a fungicide to the skin surface" (col.5 ll.23-26), because the composition provides "controlled tack and lubrication" and "**greater durability**, **protective qualities, water resistance and barrier properties**" (col. 5 ll.15-16, 20-22). The holding of an active agent, controlled lubrication, and the greater durability, protective qualities, water resistance and barrier properties would indicate to the skilled person that Kosal's composition is useful in preparations for prolonged or sustained active agent release.

Further, Kosal teaches that the hydrophilic phase of its oil-in-water emulsion contains a **thickener** or a carrier such as polyvinyl alcohol (col.4 ll.4-13) which the skilled person would recognize affects release or solubility of components in the composition. Notably the instant claims recite merely controlled or sustained release generally and no minimum duration of such release that would is clearly beyond the scope of Kosal's disclosure. Thus it is not seen that Kosal's teaching is solely limited to adhesive applications, to the exclusion of any sustained release application as Applicant contends.

In addition to these teachings in Kosal, as stated before and in the rejection above **Bott et al. teaches sustained release topical preparations of water-in-oil emulsions where the oily phase is a silicone pressure sensitive adhesive**: "[T]he silicone matrix may be comprised of a silicone pressure sensitive adhesive (silicone PSA), such as a silicate resin in silicone polymers, which can be solvent based or hot-melt, ..." (para.0041). Accordingly the obviousness rejection was not made on the ground that Kosal alone teaches attaining sustained release through the pressure sensitive adhesives. The rejection was rather based on Kosal combined with Bott et al. which teaches sustained release matrices comprising silicone PSA as well as the protein active agent recited in claim 72 (Office Action at 4, 5). Furthermore one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

9. The Applicant next argues that (i) unlike Kosal, Bott et al. teaches compositions comprising a continuous silicone phase and a discontinuous aqueous phase of a hydrophilic carrier and an active agent which would be understood by a skilled person in the art as water-in-oil compositions, whereas the present claims are drawn to compositions comprising a continuous hydrophilic phase and a discontinuous silicone phase, and thus they provide different release controlling mechanisms, and (ii) Kosal does not address sustained release of an active agent, and therefore the skilled person would not have been motivated to use Kosal's composition in combination with Bott et

al., or "at best, the skilled person might be motivated to use the Kosal silicone pressure sensitive adhesive compositions as the oil/hydrophobic phase of the water-in-oil topical preparation of Bott" (Remarks at 7, 6-8).

This argument is not persuasive for the following reasons. First, Kosal teaches an oil-in-water emulsion (disperse silicone phase in a continuous water phase, see abstract) as in the present claims, and the rejection was made over Kosal in view of Bott et al.

Second, prior to the latest amendment claim 72 had recited the potentially structural limitation "formed by mechanical inversion of a water-in-oil emulsion" which element has now been removed (without remark). Kosal teaches that preferably the oil-in-water emulsion or composition of its invention is **produced by phase inversion (col.4 ll.24-32), i.e., of a water-in-oil emulsion such as of Bott et al.** Therefore one of ordinary skill in the art would have found teaching, motivation, and suggestion to combine Kosal and Bott et al.

Regarding the mechanism of controlling release, as noted above Kosal teaches that the hydrophilic phase of the oil-in-water emulsion contains a thickener or a carrier, such as polyvinyl alcohol (col.4 ll.4-13) which the skilled person would appreciate modifies release of the active agent, e.g. a fungicide. This is parallel to the instant claims, which require that the "hydrophilic phase compris[es a protein], water, and a carrier" (see claim 72). Accordingly, absent evidence, it is not seen that the composition of Kosal et al. prepared by phase inverting the composition of Bott et al. would result in a different mechanism, not rate, of release-control. Also the instant claims recite that

the composition "comprises" the recited components and thus indicates that other ingredients may be present which the further controlling or sustaining effect.

Moreover, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Here, the examiner's position is that the skilled person would have found teaching, suggestion, and motivation to combine Kosal and Bott et al. based, in addition to the factors discussed above, on the fact that Kosal teaches phase inversion of a water-in-oil emulsion such as of Bott et al. (which recommends using pressure-sensitive adhesives as the oily phase) as a **preferred** method of preparing the oil-in-water adhesive composition of its invention, for use in durable, transdermal patches (col.4 ll.24-32; col.5 ll.20-26).

10. The Applicant's next argument is directed to dependent claims 87 – 88. The Applicant argues that in Woodard et al. the pressure sensitive adhesive layer does not contact the drug-impregnated elastomer layer 20 due to space 24, or is positioned so as to separate the drug-impregnated elastomer 20 from a patient's skin, whereas the instant claims require direct contact between the skin of a patient with the pressure sensitive adhesive located between the controlled release composition and one or more backing, cushioning, absorbent, or second adhesive layers (Remarks at 8).

This argument is not persuasive. As noted before the rejection is made as evidenced by Woodard et al. which Kosal refers to (col. 3 ll.35-38; see also the discussion above regarding claim 86). Woodard et al. states that as of the issue year of 1987, well before the instant 2003 application, multi-layer transdermal patches were "well known to those skilled in the art" (col.3 ll.33). Woodard et al. teaches that the space 24 can be "continuation of the adhesive layer 22 such that the entire skin contact surface of device 10 is coated with adhesive" (col.3 ll.25-27). Woodard et al. further teaches that the patch is pressed against the skin such that the drug-impregnated elastomer layer comes into contact with the skin (col.3 ll. 13-17). Moreover it is noted that apart from the composition of claim 72 the Applicant has failed to disclose or claim in claims 87 – 88 any feature of the multi-layer dressing that renders the claims conceivably novel over the long-known prior art transdermal patches.

11. The Applicant's last argument is directed to claim 89. The Applicant reiterates that since Kosal is silent regarding controlled release of an active agent and Bott et al. is directed to a water-in-oil emulsion, not an oil-in-water emulsion, the references are not combinable and if they were combined the claimed subject matter would not result because Bott et al. is directed to water-in-oil emulsions (Remarks at 9).

This argument is not persuasive for the same grounds stated above in sections beginning with paragraphs 8 – 10, briefly repeated as follows:

- Kosal amply and specifically discloses using the composition in prolonged medical applications such as transdermal patches, i.e., "to

hold an active material such as a fungicide to the skin surface" (col.5 ll.23-26), because the composition provides "controlled tack and lubrication" and "greater durability, protective qualities, water resistance and barrier properties" (col. 5 ll.15-16, 20-22). The holding of an active agent, controlled lubrication, and the recited properties would indicate to the skilled person that Kosal's composition is useful in preparations for prolonged or modified active agent release. Kosal also teaches that the hydrophilic phase of the oil-in-water emulsion contains a thickener or a carrier such as polyvinyl alcohol (col.4 ll.4-13) which modify release of the active agent from the composition;

- Bott et al. teaches sustained release topical preparations of water-in-oil emulsions where the external phase may be the silicone pressure sensitive adhesive such as of Kosal: "[T]he silicone matrix may be comprised of a silicone pressure sensitive adhesive (silicone PSA), such as a silicate resin in silicone polymers, which can be solvent based or hot-melt, ..." (para.0041); and
- Kosal teaches that preferably the oil-in-water emulsion or composition of its invention is preferably produced by phase inversion (col.4 ll.24-32) of a water-in-oil emulsion such as of Bott et al.

In view of the foregoing it cannot be agreed that the skilled person would not have combined Kosal with Bott et al., including the drying of the controlled-release layer

as taught by Bott et al. or that the skilled person would not have attained an oil-in-water emulsion from doing so.

CONCLUSION

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to H. SARAH PARK whose telephone number is 571-270-5258. The examiner can normally be reached on weekdays excluding alternate Wednesdays, 9 a.m. - 6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/HSP/
Examiner, Art Unit 1611

/SHARMILA G. LANDAU/

Supervisory Patent Examiner, Art Unit 1611